REMARKS

Claims 3-6 and 8-18 are pending and stand rejected under 35 USC 103(a) as unpatentable over Koyama in view of Maish, and further in view of Remington's Pharmaceutical Sciences. For at least the following reasons, applicants traverse the rejections.

As stated in response to the Office Action dated April 17, 2007, Koyama does not teach or suggest the presently claimed invention, either alone or in combination with the cited references. In fact, Koyama teaches away from the present invention.

Among other things, Koyama teaches the importance of low substituted hydroxypropylcellulose (LHPC) in its formulations. Koyama first acknowledges the drawbacks of compounding pharmaceuticals in a CF granulator. Koyama, p. 2, l. 28-36. Such methods are destructive of the spherical neutral microgranules. Koyama, p. 2, l. 37-43. To overcome that problem, Koyama proposes the addition of LHPC to the active agent mixture coating the microgranules. Koyama states that the addition of LHPC to the active agent coating during granulation "can unexpectedly yield spherical granules having enhanced granule strength and improved disintegrating property...." Koyama, p. 2, l. 40-41. "Thus, this invention relates to a process for producing granules having core, characterized in that said process comprises spraying seed granules with a dispersion of low substituted hydroxypropylcellulose, and to granules having core obtainable by said production process." Koyama, p. 2, lines 44-46.

Koyama states that "such granules may be filled into capsules by the *per se* known method, and may be mixed with other components to produce tablets." Koyama, p. 4, l. 4-6 (emphasis added). Thus, Koyama teaches that the granules

described therein must be compounded with substantial additional ingredients to be suitable for tablet formation. This is confirmed in Example 2, the only example involving the formation of a tablet.

Koyama's Example 2 describes the preparation of a formulation profoundly different than that of the instant claims. While it may be that Koyama describes the preparation of enteric coated spherical granules, Koyama teaches that those spherical granules must be admixed with almost three times their weight in "granules for tablet compression" in order to compound the formulation into a tablet.

The "granules for tablet compression" are made up of various ingredients, but they are not coated spherical granules, and they are not formed by coating neutral microgranules with less than 40 mg/g active principle and less than 1% of a compression excipient.

Specifically, Koyama describes preparing spherical granules coated with Serrapeptase and various other ingredients, and then an enteric coating. Those granules (420 g) are then admixed with almost three times their weight in "granules for tablet compression" (1440 g.).

Koyama's "granules for tablet compression" are not coated neutral microgranules as claimed here. Rather, they are a mixture of active agents and various excipients (sodium crosslinked carboxymethylcellulose, corn starch, and crystalline cellulose) that are mixed together, and then kneaded with an aqueous solution of hydroxypropylcellulose. The resulting mixture is then dried, and sieved through a 1.5 mm punching screen by use of a power mill to give granules for tablet compression. Koyama, p. 5, l. 48-56.

The "granules for tablet compression" are then mixed with the coated spherical granules at about 3:1, and compressed into tablets. Koyama, p. 5, l. 35-43.

Even if we were to look only at the Koyama coated spherical granules as described in this Example, those granules fail to satisfy the requirement that the active principle is less than 40 mg/g of the tablet. Looking only at those spherical granules, without the granules for tablet compression, the active agent of Example 2 constitutes greater than 60 mg/g active principle of those granules.

If one were to factor in the "granules for tablet compression", the quantity of active principle would be a great deal higher. Of the 1440 g. of "granules for tablet compression", more than 1,114 g is attributable to various active agents (e.g., acetominophen, chlorpheniramine maleate, noscapine, caffeine, dihydrocodeine phosphate, and di-methylephedrine hydrochloride). Thus, the active principle in the tableting composition of Koyama is almost 60% by weight of the composition. By any measure, this greatly exceeds the instant requirement that the active principle of the claimed tablet is less than 40 mg/g of tablet (i.e., 4%).

The independent claims (11, 17, and 18) all include the transitional phrase "consisting essentially of" and recite specific components. As such, those claims exclude substantial additional components that have a material effect on the properties or performance of the composition or tablet. Koyama teaches that its granules must be combined with "other components" to be suitable for tableting, and that those "other components" have a substantial role and must be present in substantial quantities. It is applicants' intention, and it is consistent with the fundamentals of claim construction, that the claims as now pending exclude such

"other components." Accordingly, Koyama does not teach or suggest the claimed invention.

Maish fails to remedy the deficiencies of Koyama. Maish is directed to a substantially different composition. As stated in applicants' response to the Office Action dated January 24, 2006, Maish describes direct compression of a carrier particulate composition comprising: (1) a cellulose carboxylic acid ester powder and (2) a lubricant. The lubricant is present in an amount between 0.25 and 5% by weight based on the total weight of the compositions (col. 3, l. 48-52). Maish does not apply the active compound as a coating to neutral microgranules. Rather, the active compound is blended as a powder with the carrier composition, and the mixture is compressed into tablets.

The tablets disclosed in Maish contain high concentrations of active compounds, e.g., 40% by weight (col. 5, lines 21-24). In contrast, the claimed tablets have very low concentration of active principle, i.e., less than 40 mg/g. One skilled in the art seeking to formulate tablets having very low concentration of active principle would not have been motivated to look to a reference such as Maish, which discloses tablets having high concentrations of active agent.

Furthermore, the rejection fails to identify how or why one skilled in the art would have combined the teachings of Koyama with those of Maish to arrive at the present invention. Koyama is expressly directed to solving a problem associated with the fracturing of spherical cores when coated and compounded in a centrifugal fluidized-bed coating-granulator ("CF granulator"). Koyama, p. 2, l. 17-36. Koyama's principal objective is the preparation of compositions that can be compounded in capsules. Although the compositions may be tableted, the requisite additives and

excipients that must be combined with the coated spherical granules produce compositions that neither resemble nor suggest the compositions of the claimed invention.

Maish, on the other hand, is directed to producing tableting compositions that afford high concentrations of active agents that are notorious for poor tableting properties: compressibility, friability, and tablet ejection, e.g., acetominophen. Maish, col. 2, l. 44-49. Maish is a reference one might turn to if one wanted to increase, rather than decrease, the quantity of active principle in the formulation. The instant invention, however, is in fact directed to formulations of decreased quantities of active principle, i.e., less than 40 mg/g (<4% by weight). Thus, one skilled in the art addressing the objectives of the instant invention would not have turned to Maish for guidance in developing new tableting compositions.

Further, Maish does not describe the use of the neutral microgranules of the instant claims. Instead, Maish, which is expressly directed to the preparation of tablets, urges the use of microcrystalline cellulose. The microscrystalline cellulose of Maish is also not coated as are the instantly claimed neutral microgranules, but is instead commingled with the active principle, and then compressed into tablets. There has been no showing why one of skill in the art, even if combining the teachings of these two references, would have favored coating neutral microgranules rather than commingling with the microcrystalline cellulose of Maish.

Indeed, it is much more likely that one skilled in the art, considering these two references in their entirety, would have followed the compounding technique of Maish, i.e., commingling with microcrystalline cellulose. And even if one had been motivated to use the techniques and compositions of Koyama, that skilled worker

would have understood the formulations would have required substantial additional components to produce a useful tablet, and such components would have taken the compositions and tablets outside the scope of the instant claims. Accordingly, the two references, taken together, fail to teach or suggest the claimed invention.

Remington's Pharmaceutical Sciences likewise fails to cure the deficiencies of either Koyama, or Koyama in combination with Maish. Remington's is relied upon only as providing a disclosure of lubricants. The cited disclosure proposes formulations wherein the lubricant is between 0.1 and 5%; and wherein most of the lubricants, except talc, are used in concentrations less than 1%. This alone fails to cure the deficiencies of Koyama and Maish.

Even if Remington's were to suggest applicants' singular element of the claimed lubricant - a point applicants do not concede - the cited reference still falls short of suggesting the claimed invention as a whole, alone or in combination. Nothing cited in the reference suggests the use of the claimed neutral microgranules, the low concentration of active principle, or the exclusion of other substantial ingredients. There is no showing that one skilled in the art would have been motivated to formulate the compositions or tablets of the instant claims, and, even if so motivated, there is no showing that such skilled worker would have actually arrived at the compositions or tablets of the instant claims. Thus, the rejection fails to make a *prima facie* case of obviousness, and applicants request reconsideration and withdrawal of the rejection.

CONCLUSION

In view of the foregoing amendments and remarks, applicants respectfully request reconsideration and withdrawal of all outstanding rejections. Applicants submit that the claims are now in condition for allowance, and respectfully request formal notification to that effect. If, however, the Examiner perceives any impediments to such a notice of allowability, whether substantive or formal, the Examiner is encouraged to call Applicants' attorney at the number provided below. Such informal communication will expedite examination and disposition of this case.

Respectfully submitted,

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Date: Sept. 11, 2008

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